Complementary prognostic value of pelvic magnetic resonance imaging and whole-body fluorodeoxyglucose positron emission tomography/computed tomography in the pretreatment assessment of patients with cervical cancer

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Abstract: OBJECTIVE: The aim of this study was to evaluate the incremental prognostic value of pelvic magnetic resonance imaging (MRI) and whole-body F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) findings compared with clinical-histopathologic factors in patients with newly diagnosed cervical cancer. METHODS: The institutional review board approved this retrospective study of 114 patients (median age, 40.6 years) with International Federation of Gynecology and Obstetrics (FIGO) stage I-IVB cervical cancer who underwent pretreatment MRI and PET/CT. All scans were reviewed for locoregional tumor extent, pelvic or/and para-aortic lymphadenopathy, and distant metastases. Univariate Cox proportional hazard regression was performed to evaluate associations between clinical-histopathologic factors, imaging findings, and progression-free survival (PFS). Multivariate models were built using independent predictors for PFS. Harrell C was used to measure concordance (C index). RESULTS: Forty patients progressed within a median time of 10.4 months (range, 0.4-40.3 months). At univariate analysis, age, FIGO stage, tumor histology, tumor grade, and all MRI and PET/CT features were significantly associated with PFS ($P < 0.0001$ to $P = 0.0474$). A multivariate model including clinical and imaging parameters (parametrial invasion on MRI and para-aortic lymphadenopathy/distant metastases on PET/CT) had significantly higher concordance for predicting PFS than a model including clinical parameters only (C index: 0.81 [95% confidence interval, 0.75-0.87] vs 0.68 [95% confidence interval, 0.59-0.78]; $P < 0.001$). The comparison of C indices for the combined clinical and imaging model approached significance when compared with a FIGO stage model (C index: 0.81 [95% confidence interval, 0.75-0.87] vs 0.75 [95% confidence interval, 0.69-0.82]; $P = 0.058$). CONCLUSIONS: In patients with newly diagnosed cervical cancer, a prognostic model including combined MRI and PET/CT findings provides information that complements clinical and histopathologic factors.

DOI: https://doi.org/10.1097/IGC.0000000000000519

Complementary prognostic value of pelvic magnetic resonance imaging and whole-body fluorodeoxyglucose positron emission tomography/computed tomography in the pretreatment assessment of patients with cervical cancer. International Journal of Gynecological Cancer, 25(8):1461-1467.
DOI: https://doi.org/10.1097/IGC.0000000000000519

Complementary Prognostic Value of Pelvic Magnetic Resonance Imaging and Whole-Body Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in the Pretreatment Assessment of Patients With Cervical Cancer

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Objective: The aim of this study was to evaluate the incremental prognostic value of pelvic magnetic resonance imaging (MRI) and whole-body ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) findings compared with clinical-histopathologic factors in patients with newly diagnosed cervical cancer.

Methods: The institutional review board approved this retrospective study of 114 patients (median age, 40.6 years) with International Federation of Gynecology and Obstetrics (FIGO) stage I-IVB cervical cancer who underwent pretreatment MRI and PET/CT. All scans were reviewed for locoregional tumor extent, pelvic or/and para-aortic lymphadenopathy, and distant metastases. Univariate Cox proportional hazard regression was performed to evaluate associations between clinical-histopathologic factors, imaging findings, and progression-free survival (PFS). Multivariate models were built using independent predictors for PFS. Harrell *C* was used to measure concordance (*C* index).

Results: Forty patients progressed within a median time of 10.4 months (range, 0.4–40.3 months). At univariate analysis, age, FIGO stage, tumor histology, tumor grade, and all MRI and PET/CT features were significantly associated with PFS ($P < 0.0001$ to $P = 0.0474$). A multivariate model including clinical and imaging parameters (parametrial invasion on MRI and para-aortic lymphadenopathy/distant metastases on PET/CT) had significantly higher concordance for predicting PFS than a model including clinical parameters only (*C* index: 0.81 [95% confidence interval, 0.75–0.87] vs 0.68 [95% confidence interval, 0.59–0.78]; $P < 0.001$). The comparison of *C* indices for the combined clinical and imaging model approached significance when compared with a FIGO stage model (*C* index: 0.81 [95% confidence interval, 0.75–0.87] vs 0.75 [95% confidence interval, 0.69–0.82]; $P = 0.058$).

Conclusions: In patients with newly diagnosed cervical cancer, a prognostic model including combined MRI and PET/CT findings provides information that complements clinical and histopathologic factors.

Key Words: Prognostic value, Pelvic MRI, Whole-body FDG PET/CT, Cervical cancer

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ISSN: 1048-891X
DOI: 10.1097/IGC.0000000000000519

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The authors declare no conflicts of interest.

Received October 30, 2014, and in revised form May 5, 2015.
Accepted for publication May 31, 2015.

(*Int J Gynecol Cancer* 2015;25: 1461–1467)

In patients with newly diagnosed cervical cancer, the prediction of prognosis is currently based on the International Federation of Gynecology and Obstetrics (FIGO) clinical staging system, which has its known limitations.[1,2] The survival rate of patients with the same FIGO stage may vary[3]; therefore, FIGO stage alone may not be entirely satisfactory to accurately provide prognostic information in patients with cervical cancer. The prognostic relevance of other pretreatment clinical-histopathologic variables such as patient's age, tumor histology and grade, tumor diameter, deep stromal and parametrial invasion, lymph vascular invasion, and lymph node (LN) metastases has also been evaluated. In a study of 187 patients with stage IB2-IIB cervical cancer, pathologically assessed parametrial invasion and LN status were predictors of disease-free survival and overall survival (OS)[4] independent of other clinical-histopathologic factors.

Few previous reports have simultaneously analyzed the prognostic value of multiple variables (including imaging findings) in patients with cervical cancer to create a nomogram able to provide individualized prediction of outcome.[5–9] These nomograms, which include age, histological subtype, tumor size, parametrial involvement, pelvic organ invasion, and LN status, have been shown to compare favorably with FIGO staging system. In patients with locally advanced cervical cancer (LACC), Kang et al[5] developed a 4-parameter risk assessment model to predict recurrence, which included pelvic/para-aortic LN metastasis detected on ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) and clinical-histopathologic factors. In contrast, Shim et al[9] introduced a 3-variable risk assessment model to predict 5-year survival in patients with LACC, which incorporated histology, tumor size, and para-aortic LN metastasis detected on magnetic resonance imaging (MRI). Both nomograms showed high accurate prediction, and their use as an alternative to FIGO stage system has been suggested. However, the prognostic value of combining information derived from MRI, FDG PET/CT, and clinical-histopathologic parameters in patients with all-stage cervical cancer has not been reported. This information is particularly important with the recent introduction of integrated PET/MRI scanners in clinical use. Positron emission tomography/MRI is able to provide integrated anatomic, metabolic, and functional information. In the future, specific PET/MRI acquisition and interpretation protocols that provide information useful to predict clinical outcomes in patients with cervical cancer need to be developed. Hence, the aims of our study were to (1) evaluate the prognostic value of pelvic MRI, whole-body FDG PET/CT, and clinical-histopathologic factors in the pretreatment assessment of patients with FIGO stage I to IV cervical cancer and (2) assess the added value of a combined MRI and whole-body FDG PET/CT qualitative imaging parameters and clinical-histopathologic factors, compared with clinical-histopathologic factors alone.

MATERIALS AND METHODS

The institutional review board approved and issued a waiver of informed consent for this retrospective study, which was compliant with the Health Insurance Portability and Accountability Act.

Patient Cohort

Review of our prospectively maintained uterine cervical cancer database identified 116 patients with pathologically proven cervical cancer who underwent pelvic MRI and FDG PET/CT for initial staging prior to primary treatment (surgery and/or chemoradiotherapy) at our institution between November 2005 and May 2012. Two patients were excluded from the analysis because no follow-up information was available; thus, our study cohort included 114 patients. Forty-nine patients have been included in a previous published study evaluating the use of quantitative FDG uptake (PET) and diffusion (MRI) metrics in the assessment of cervical cancer.[7]

Imaging Protocol

Magnetic resonance imaging was performed on a 1.5-T (Signa or Discovery MR450; GE Medical Systems, Milwaukee, WI) or 3-T (Signa HDxt or Discovery MR750; GE Medical Systems) system using a body coil for excitation and a multichannel phased-array coil for signal reception. Specific MRI parameters varied during the study period, following changes in our standard clinical protocol, but all examinations included an axial T1-weighted fast-spin-echo sequence and T2-weighted fast-spin-echo sequences in 3 imaging planes (axial/sagittal/axial oblique perpendicular to the cervix). Contrast-enhanced MRI scans were obtained with a 3-dimensional spoiled gradient-pulse T1-weighted LAVA (liver acquisition volume acceleration) sequence before and after administration of 0.1 mmol/kg of gadolinium at a rate of 2 mL/s, which was followed by a 20-mL saline bolus injection.

All patients were scanned on dedicated PET/CT systems (Discovery STE, LS, or 690 [GE Medical Systems]; Biograph 16 [Siemens Medical Systems]). A clinical imaging protocol was applied with injection of 400 to 455 MBq FDG after 6-hour fasting and blood glucose level of less than 200 mg/dL followed by approximately 60-min uptake period. Subsequently, a low-dose, attenuation correction CT scan (120–140 kV, 80 mA) was acquired, followed by PET emission images from the midthighs to skull base.

Images Analysis and Interpretation

Magnetic resonance imaging and FDG PET/CT examinations were retrospectively reviewed by a radiologist with 5 years of experience in gynecologic cancer imaging, using our institution's Picture Archiving and Communication System (Centricity; GE Medical Systems). The reader was blinded to clinical and histopathologic information. The reader evaluated all MRIs, followed by the PET/CTs. The reader recorded orthogonal tumor diameters; the distance between the tumor and internal cervical os; the presence of cervical stromal invasion; parametrial involvement; vaginal extension (lower one third and upper two thirds); bladder, rectum, and/or pelvic sidewall invasion; presence of pelvic and/or para-aortic lymphadenopathy; and distant metastasis. The 3 orthogonal tumor diameters were measured on axial and sagittal fast-spin-echo T2-weighted images (T2WIs). On MRI, diagnostic criteria of parametrial invasion were full-thickness disruption of the normal T2WI hypointense cervical stroma, spiculated tumor-parametrium interface (referred to as spiculated tumor), soft-tissue extension into the parametria, or encasement of the periuterine vessels. Vaginal extension was diagnosed when an interruption of the normal T2WI hypointense vaginal wall was observed. On MRI, bladder and/or rectal involvement was diagnosed when an interruption of the normal T2WI hypointense bladder or rectal wall was observed, with tumor nodules seen in the mucosal layer on T2WI. On MRI, diagnostic criterion for pelvic sidewall invasion was tumor extending within 3 mm and abutting the obturator internus or piriformis muscles, with concomitant loss of the normally present intervening fat planes.

On PET/CT, bladder or rectum involvement was diagnosed when direct contact between the FDG avid tumor and the organ was observed, with concomitant absence of a fat plane evidenced on the CT component of the examination. Similarly, pelvic sidewall invasion was diagnosed in the presence of direct contact between the FDG avid tumor and obturator internus and/or piriformis muscle.

On MRI, pelvic and para-aortic LNs were considered metastatic if their short axis were more than 1 cm, or more than 0.8 cm if they had irregular borders and/or round shape. Lymph nodes showing FDG uptake above the background activity on PET images were considered metastatic. Focal areas of FDG uptake above the background activity located in the liver, lung, and thorax were considered distant metastasis. Each of the imaging features pertaining to the regional tumor spread, nodal involvement, and distant metastases were assessed on a qualitative 1- to 5-point scale as follows: 1 = definitely absent, 2 = probably absent, 3 = indeterminate, 4 = probably present, and 5 = definitely present. Any imaging feature scored as 4 or 5 was considered a positive finding.

Outcome Data

One of the authors reviewed the patients' electronic medical records. All patients were evaluated after treatment every 3 months until death or last contact. Progression of disease was defined as the presence of tumor at biopsy or disease progression on follow-up imaging according to RECIST (Response Evaluation Criteria in Solid Tumors) 1.1.[10]

Statistical Analysis

Descriptive statistics were calculated, including frequencies and percentages for categorical variables and medians and ranges for continuous variables. For the purpose of analysis, FIGO stage was grouped into I-IIA versus IIB-IVB, grade (G) was grouped as 1/2 versus 3, and histology was dichotomized as squamous cell carcinoma (SCC) versus non-SCC. Pathological FIGO stage was used in patients who underwent surgery instead of pretreatment clinical FIGO stage. Age at diagnosis, maximum tumor diameter on MRI, and tumor volume were evaluated as continuous measurements. Organ involvement on MRI and PET/CT was categorized as positive or negative. Para-aortic LN metastasis and distant metastases detected on PET/CT were combined to indicate disease outside the pelvis. Imaging parameters with 10 or more positive cases were included in the analysis.

Univariate Cox proportional hazard regression was used to assess the relationship between imaging parameters and progression-free survival (PFS). Given the limited number of events, only a bivariate model could be built for OS, which would not allow for sufficient assessment of imaging parameters' incremental value. Therefore, only PFS was assessed at the univariate and multivariate levels. The 2 modalities, MRI and PET, were analyzed separately. We used the methods of Lin et al[11] to assess the proportional assumption. Progression-free survival was defined as the interval between first imaging date and date of last follow-up, date of death, or date of first progression. Patients free of pelvic and extrapelvic disease and alive at last follow-up were censored. $P < 0.05$ was considered statistically significant.

Multicolinearity was assessed using Spearman correlations. Any 2 variables with a correlation, $\rho > 0.50$ were considered nonindependent and not included in multivariate analysis. Variables significant at $P < 0.05$ on univariate analyses and clinically meaningful prognostic indicators were considered for multivariate analysis. Multivariate analyses were performed for PFS using Cox proportional hazards regression. We used the standard event per variable rule developed by Peduzzi et al[12] to determine the maximum number of parameters allowed in the multivariate model.

Based on prior clinical prognostic indicators, age and grade comprised our baseline clinical model. Parametrial invasion on MRI and para-aortic lymphadenopathy/distant metastasis were added to create the full model. The multivariate models' discriminatory ability was calculated using the concordance index (*C* index), Harrell *C*, with jackknife 95% confidence intervals (CIs). We compared the *C* indices of the multivariate model including clinical and imaging parameters with the model including clinical parameters only and the FIGO stage model. As this was a retrospective, exploratory study, no corrections were made for multiple hypothesis testing. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC) and Stata SE 12 (StataCorp, College Station, TX).

RESULTS

Patients Characteristics

Patient characteristics are summarized in Table 1. The median age at diagnosis was 40.1 years (range, 18.2–88.9

TABLE 1. Clinical and pathologic patient characteristics

Continuous Variables	Median	Min-Max
Age at diagnosis, y	40.64	18.22–88.93
Time between scans, d	3	0.00–50.00
Time to progression, mo (n = 40)	10.4	0.36–40.34
Categorical Variables	**n**	**%**
Histology		
Non-SCC	49	42.98
SCC	65	57.02
Grading		
Grade 1/2	67	58.77
Grade 3	47	41.23
FIGO stage		
I-IIA	60	52.63
IIB-IVB	54	47.37
Death		
Alive	90	78.95
Dead	24	21.05
Progression		
No	74	64.91
Yes	40	35.09
Treatment		
CRT only	50	43.86
Surgery only	37	32.46
Surgery + CRT	27	23.68

years), and the median time between MRI and PET/CT was 3 days (range, 0–50 days). Patients were treated per standard of care at our institution with surgery alone (32.5%), chemoradiation-therapy (CRT) alone (43.9%), or surgery and CRT (21.0%). The median follow-up time was 25.8 months (range, 0.3–84.8 months). The median time to progression was 10.4 months (range, 0.4–40.3 months). At the end of follow-up, 24 patients had died of disease (21.1%), and an additional 16 patients progressed but were alive (14.0%).

Progression-Free Survival

Univariate Analyses

FIGO stage ($P < 0.0001$), age at diagnosis ($P = 0.0001$), tumor grade ($P = 0.0455$), and histology ($P = 0.0017$) were significantly associated with PFS. Patients with FIGO stage IIB-IVB, tumor grade 3, and increased age were at increased risk for progression. All MRI and PET/CT parameters assessed were associated with PFS: distance of tumor to the internal cervical os on MRI ($P = 0.0474$), maximum diameter on MRI ($P < 0.0001$), tumor volume ($P < 0.0001$) on MRI, parametrial invasion on MRI ($P < 0.0001$), spiculated tumor on MRI ($P < 0.0001$), vessel encasement on MRI ($P < 0.0001$), vaginal invasion on MRI ($P < 0.0001$), bladder invasion on MRI ($P < 0.0001$), pelvic sidewall invasion on PET and MRI ($P < 0.0001$ for both), pelvic lymphadenopathy on PET and MRI ($P < 0.001$ for both), and para-aortic lymphadenopathy/distant metastases on PET ($P < 0.0001$). Presence of features or positivity of invasion increased the risk of progression, (Table 2).

Multivariate Analyses

Our statistical design allowed a maximum of 4 variables to be used in multivariate analysis (Table 3). Multicolinearity was present among pelvic sidewall invasion, parametrial invasion, pelvic lymphadenopathy, spiculated tumor, tumor volume, maximum diameter, and vaginal involvement location, indicating a lack of independence among these parameters. Therefore, based on clinical significance and prognostic indication on univariate analyses, parametrial invasion was chosen to represent the MRI parameters. Para-aortic lymphadenopathy/distant metastasis assessed on PET/CT was chosen to represent PET/CT parameters given its relative independence and clinical importance.

Based on prior clinical prognostic indicators, age and grade comprised our baseline clinical model. Age ($P = 0.0001$) and grade ($P = 0.0315$) were both significant in the multivariate model with a C index of 0.68 (95% CI, 0.59–0.78). When parametrial invasion on MRI and para-aortic lymphadenopathy/distant metastasis were added to create the full model, only grade ($P = 0.0375$), parametrial invasion ($P = 0.005$), and para-aortic lymphadenopathy/distant metastasis ($P = 0.0395$) remained significant. The concordance index rose to 0.81 (95% CI, 0.75–0.87), which was significantly different from the baseline clinical model ($P < 0.001$). This indicated that imaging parameters add significant incremental value to clinical prognostic indicators. We then compared the concordance index of the model of FIGO Stage alone to the full model and this difference approached significance ($P = 0.058$).

DISCUSSION

In this study, we demonstrated a significant incremental prognostic value of pretreatment MRI and FDG PET/CT findings to clinical and histopathologic prognostic indicators in patients with newly diagnosed cervical cancer. When imaging findings were incorporated into a multivariate model together with clinical-histopathologic factors, the concordance index was significantly higher than a model with clinical factors alone, indicating that the full model that includes pretreatment imaging findings had superior alignment between the predicted and observed survival times. Similar to our findings, previous studies showed more accurate predictive ability of models that included qualitative imaging parameters and clinical-pathological factors compared with FIGO stage alone. However, these studies focused only on high-risk cohorts of patients with LACC treated with definitive CRT,[5,13] thus unable to construct a prognostic model, which is, by definition, independent of treatment received. Only 1 previous study constructed and validated a prognostic model of clinical-pathological factors alone (with no added imaging findings) in a large cohort of cervical cancer patients including FIGO stage I to IV.[8] In another study of 187 patients with stage IB2-IIB cervical cancer, Gadducci et al[4] found that

TABLE 2. Univariate cox proportional hazards regression for PFS

PFS			n	Progressed	Hazard Ratio	95% CI	*P*
Clinical parameters	Variable	Level					
	Age at diagnosis		114	40	1.04	1.02–1.06	**<0.0001**
	Histology	SCC	65	31	3.28	1.56–6.90	**0.0017**
		Non-SCC	49	9	REF		
	Grading	Grade 3	47	20	1.89	1.01–3.52	**0.0457**
		Grade 1/2	67	20	REF		
MRI parameters	FIGO stage	IIB-IVB	54	35	12.07	4.70–30.98	**<0.0001**
		I-IIA	60	5	REF		
MRI	Tumor to internal cervical o's distance		113	40	0.94	0.88–1.00	**0.0472**
	Maximum diameter		114	40	1.04	1.03–1.05	**<0.0001**
	Tumor volume		114	40	1.01	1.00–1.01	**<0.0001**
	Spiculated tumor	Yes	63	35	8.04	3.14–20.59	**<0.0001**
		No	51	5	REF		
	Vessel encasement	Yes	26	21	6.13	3.26–11.52	**<0.0001**
		No	88	19	REF		
	Parametrial invasion	Positive	66	38	19.54	4.71–81.13	**<0.0001**
		Negative	48	2	REF		
	Vaginal invasion location	Lower one third	5	5	25.92	7.34–91.59	**<0.0001**
		Upper two thirds	55	30	8.79	3.40–22.72	**<0.0001**
		None	54	5	REF		
	Pelvic Sidewall Invasion	Positive	38	29	8.22	4.07–16.57	**<0.0001**
		Negative	76	11	REF		
	Bladder Invasion	Positive	13	12	5.93	2.97–11.80	**<0.0001**
		Negative	101	28	REF		
	Pelvic LN involvement	Positive	60	32	5.5	2.51–12.06	**<0.0001**
		Negative	54	8	REF		
PET/CT parameters	Pelvic sidewall invasion	Positive	17	14	4.21	2.18–8.14	**<0.0001**
		Negative	97	26	REF		
PET	Pelvic LN involvement	Positive	45	28	5.21	2.64–10.30	**<0.0001**
		Negative	69	12	REF		
	Para-aortic LN/distant metastasis	Positive	16	13	5.12	2.59–10.11	**<0.0001**
		Negative	98	27	REF		

pathologically assessed parametrial invasion and LN status were predictors of disease-free survival and OS independent of other clinical-histopathologic factors. In contrast, in our study, MRI assessment of parametrial invasion and LN status on PET/CT were predictors of PFS. This is important as MRI is widely used to assess parametrial invasion and PET/CT to assess LN status prior to treatment decision (surgery vs radiotherapy). For example, patients with findings of parametrial invasion on MRI do not usually undergo surgery; they have radiotherapy instead, so histological confirmation is not possible in all cases. To the best of our knowledge, our study is the first to investigate the incremental prognostic value of combined MRI and FDG PET/CT qualitative parameters and clinical-pathological factors compared with clinical-pathological factors alone in the pretreatment assessment of patients with all-stage cervical cancer.

In patients with newly diagnosed cervical cancer, the prognostic prediction is currently based on FIGO staging system. International Federation of Gynecology and Obstetrics stage is based on clinical examination, and the system's limitations have been described.[1,2] Moreover, the risk of recurrence in patients with early stage of disease has been reported to range between 5% and 30%.[14] Polterauer and colleagues[8] built a nomogram incorporating FIGO stage, patient's age, tumor histology, LN status, tumor size, and parametrial invasion to predict survival in patients with stage I-IV. We found that the prognostic ability of models including MRI and FDG PET/CT parameters was higher than FIGO

TABLE 3. Multivariate Cox modeling for PFS

Multivariate Models						
			Hazard Ratio	95% CI	*P*	C Index (95% CI)
Model	Variable	Level				
FIGO	FIGO stage	IIB-IVB	12.07	4.70–31.01	<0.0001	0.75 (0.69–0.82)
		I-IIA	REF			
Clinical	Age at diagnosis		1.04	1.02–1.07	0.0001	0.68 (0.59–0.78)
	Grade	Grade 3	1.99	1.06–3.73	0.0315	
		Grade 1/2	REF			
Full	Age at diagnosis		1.02	1.00–1.05	0.08	0.81 (0.75–0.87)
	Grade	Grade 3	1.98	1.04–3.75	0.0375	
		Grade 1/2	REF			
	Parametrial invasion on MRI	Positive	13.1	3.06–56.16	0.0005	
		Negative	REF			
	Para-aortic LN/distant metastasis on PET	Positive	2.08	1.04–4.18	0.0395	
		Negative	REF			

stage alone. Although the difference in concordance indices between the FIGO stage and full model incorporating imaging parameters (0.75 vs 0.81) did not reach significance ($P = 0.058$), this level of improvement in *C* indices is considered substantial and lends credence to the possibility that the small number of events may explain the lack of significance. Previous studies have indicated that FIGO staging may be influenced by MRI findings especially in patients who undergo radiotherapy, and parametrial invasion cannot be assessed at pathology; thus, it may be difficult to retrospectively assess the independent predictive ability of these variables.[1]

Maximum tumor diameter was an independent prognostic factor for PFS in our study. Tumor diameter is an established prognostic parameter[15,16] in cervical cancer and correlates well with other pathological prognostic factors, especially with parametrial involvement.[17] Parametrial involvement significantly influences outcome of patients with cervical cancer,[18] and the assessment of parametrial involvement is crucial for the primary treatment. Therefore, it was included in our prognostic 4-factor model. Parametrial spread may be detected at histopathology even in women with early FIGO stage,[19] and it has been reported to be related with other adverse prognostic factors, such as higher histological grade, tumor size, and metastasis to pelvic LN.[17] In early invasive cervical cancers extended to parametria and para-aortic LN at surgical staging, patients' survival was reported to be irrespective of other clinical-pathological factors, such as histological subtypes.[18] Our study supports the previous results.[8,18] Importantly, we showed that parametrial invasion assessed noninvasively on MRI was the most robust prognostic factor for PFS, exceeding the prognostic ability of other clinical-histopathologic factors.

In our study, the presence of pelvic LN metastasis on imaging was a predictor PFS in the univariate analysis, and para-aortic lymphadenopathy/distant metastases was a significant predictor of PFS on both univariate and multivariate analyses. Many authors have reported that the presence of pelvic/para-aortic LN metastases has an effect on patient's survival. Nonetheless, the prognostic importance of LN status assessed on imaging is still controversial in cervical cancer.[5,9] Some studies show that pelvic/para-aortic LN metastasis assessed on FDG PET/CT is an independent predictive factor for PFS in LACC.[5,13] Kang et al[5] introduced a model to predict distant recurrence in patients with LACC, including histology, tumor size, and pelvic/para-aortic LN metastasis on FDG PET/CT. The concordance index (0.73) was superior to that of FIGO stage alone (0.57). Shim et al[9] showed that para-aortic LN metastasis on MRI, but not ^{18}F-FDG PET/CT, was an independent predictor of OS in patients with cervical cancer. The concordance index of this model (0.69) was superior to that of FIGO stage alone (0.59). It is important to note that the *C* indices in our study were much higher than those previously published.

Combined MRI and FDG PET/CT have been shown to improve triage to the most appropriate primary therapy in patients with early-stage cervical cancer.[20] The prediction of progression or recurrence in individual patients before any therapy has started would add clinical value as a "risk assessment model" including MRI and FDG PET/CT findings can provide prognostic information that complements clinical and histopathologic factors. This information is important as currently combined PET/MRI equipment is becoming an available tool for staging patients with gynecologic malignancies. In this setting, PET/MRI protocols will need to be balanced between high-resolution imaging of the pelvis that provides crucial information on local disease extent (especially presence of parametrial invasion) and whole-body PET/CT that provides valuable information on nodal and distant metastasis. Encouraging preliminary results have been reported in multiple malignancies using whole-body MRI techniques; however, further work is needed to evaluate its added value in gynecologic malignancies.

Our study has several limitations. First, it is a retrospective study; hence, many factors could not be controlled

for, including the influence of MRI findings on FIGO stage especially in the subset of patients who underwent radiotherapy, and thus, pathological FIGO stage could not be obtained. Second, the retrospective nature allowed for a heterogeneous population, including patients who underwent different treatment modalities. However, the aim of our study was to evaluate potential prognostic value of multiple MRI and FDG PET/CT findings, which are, by definition, independent of treatment received. Third, a single reader evaluated both MRI and FDG PET/CT scans. Although this makes evaluation or interobserver variability impossible, it matches routine clinical practice where a single experienced reader specialized in gynecology-oncology imaging reports the majority (>80%) of these studies and reviews them at the weekly tumor board meeting. Finally, subsequent validation of our results is warranted and should include a per-patient measure such as a nomogram; at present, the best way to interpret our results is that they support the notion that both MRI and PET/CT provide complementary information.

CONCLUSIONS

In pretreatment assessment of patients with cervical cancer, a prognostic model including combined MRI and FDG PET/CT findings in addition to clinical-pathological factors adds significant incremental value to clinical-pathological factors alone.

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